



CODEN [USA]: IAJ PBB

ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

<https://doi.org/10.5281/zenodo.23243220>Available online at: <http://www.iajps.com>

Research Article

**A PROSPECTIVE STUDY ON EFFECT OF
CEPHALOSPORIN IN BACTERIAL INFECTION****Yerra Praveena, Ch. Sunitha**Department Of Pharmacy Practise ,Princeton College Of Pharmacy, Pocharam, Hyderabad,
Telangana 500088.**Abstract:**

Most bacteria aren't harmful. In fact, we have many bacteria inside our body and on our skin. Bacteria in our intestines (gut) help us to digest our food. But some bacteria can cause infections. Bacterial infections can affect many parts of your body, including. A bacterium is a single, but complex, cell. It can survive on its own, inside or outside the body. Escherichia coli is the second cause of bacterial meningitis in neonates. Despite the use for 35 years of third-generation cephalosporins, high morbidity and mortality rates with E. coli meningitis continue to occur. Because cephalosporins has good microbiologic activity against E. coli and good penetration in cerebrospinal fluid and brain. Antibiotic therapy recommended for meningitis due to E. coli like third generation cephalosporin.. However, drawbacks are low tissue penetration and reduced bactericidal activity on microorganisms in the stationary phase. Corticosteroids are not currently recommended in the treatment of neonatal meningitis All neonates (<1 month of age) and infants (<one year of age) with a showed diagnosis of E. Coli meningitis were covered. The prognosis of meningitis was primarily based on as a minimum one of the following: fantastic CSF subculture, presence of superb soluble antigens in CSF, effective PCR consequences for CSF and/or fine blood culture related to pleocytosis (≥ 30 cells/ μ L) in CSF. This study suggests that third generation cephalosporins at least offers some advantage in terms of improving short-term neurologic outcomes and mortality.

Keywords: Escherichia coli, Cephalosporins, pharmacokinetics, pharmacodynamics, CSF.

Corresponding author:**Yerra Praveena,**Department of of Pharmacy Practice, Princeton college of Pharmacy,
Pocharam, Hyderabad

Mobile:

Email Id: Id-princeton.pharmacy@gmail.com

QR CODE



Please cite this article in press **Yerra Praveena et al., A Prospective Study On Effect Of Cephalosporin In Bacterial Infection., Indo Am. J. P. Sci, 2026; 13(10).**

INTRODUCTION:

A bacterium is a single, but complex, cell. It can survive on its own, inside or outside the body.

Most bacteria aren't harmful. In fact, we have many bacteria inside our body and on our skin. Bacteria in our intestines (gut) help us to digest our food.

But some bacteria can cause infections. Bacterial infections can affect many parts of your body, including: ^[2]

- throat
- lungs
- skin
- bowel

Many infections are mild, but some are severe.

Some examples of bacterial infections are:

- Legionnaires' disease
- meningococcal disease
- Q fever
- strep throat
- tuberculosis (TB)
- whooping cough (pertussis) ^[3-5]

Other causes of infectious diseases are viruses, parasites and fungi.

What are the symptoms of a bacterial infection?

The symptoms of a bacterial infection depend on the location of your infection and the type of bacteria involved.

There are some general signs of bacterial infection:

- fever
- feeling tired
- swollen lymph nodes in your neck, armpits, groin or elsewhere
- headache
- nausea or vomiting

Bacterial infections occur when bacteria enter your body. Once in your body they increase in number.

This causes an immune reaction in your body.

Bacteria can enter your body through:

- a cut on your skin
- eating or drinking contaminated food or water
- breathing in droplets from an infected person
- touching dirty surfaces and then touching your eyes, nose, or mouth

Bacteria can also be transmitted by contact with blood and other bodily fluids.

Bacterial infections and weather events

The risk of getting a bacterial infection increases when you are in contact with flood water. Flood water can come from storms or cyclones ^[6].

Touching items affected by flooding can also increase your risk of bacterial infection. You should avoid contact with flood water and practice good hand hygiene. Wash your hands with soap and clean water. If clean water isn't available, use hand sanitiser.

- Serious bacterial infections can be effectively treated with antibiotics. These medicines either kill the bacteria or stop them multiplying. This helps your body's immune system fight the bacteria.
- Choice of antibiotic will depend on the bacteria that is causing your infection.
- Antibiotics that work against a wide range of bacteria are called broad-spectrum antibiotics.
- Antibiotic resistance is a growing problem so antibiotics must always be used appropriately and as prescribed.

Bacterial infections can be highly contagious. Bacterial infections are spread between people through: ^[7]

- coughing
- sneezing
- vomiting
- bodily fluids, from sex or sharing dirty needles

Special care to avoid spreading infections by: ^[8]

- washing your hands properly
- covering up when sneezing and coughing
- not sharing cups and drink bottles
- having safe sex
- not sharing needles

Complications ^[9]

It's important to seek treatment because untreated bacterial infections can lead to serious problems. For example, an untreated infected cut can cause cellulitis, a spreading skin infection.

Untreated bacterial infections can sometimes lead to serious, life-threatening conditions.

- **Septicaemia** is a serious blood infection. It is when bacteria enter the bloodstream and cause blood poisoning.
- **Sepsis** is a condition that happens when the body damages its own tissues in response to a bad infection. Sepsis can cause shock, organ failure and death if it's not treated quickly.

Sepsis is a medical emergency and can be fatal if not treated quickly. If you suspect you or someone else has sepsis, call triple zero (000) for an ambulance.

Escherichia coli (E. coli) bacteria normally live in the intestines of healthy people and animals. Most types of E. coli are harmless or cause relatively brief diarrhea. But a few strains, such as E. coli O157:H7, can cause severe stomach cramps, bloody diarrhea and vomiting. ^[11-13]

You may be exposed to E. coli from contaminated water or food — especially raw vegetables and undercooked ground beef. Healthy adults usually

recover from infection with *E. coli* O157:H7 within a week. Young children and older adults have a greater risk of developing a life-threatening form of kidney failure

SYMPTOMS: ^[14]

Signs and symptoms of *E. coli* O157:H7 infection usually begin three or four days after exposure to the bacteria. But you may become ill as soon as one day after exposure to more than a week later. Signs and symptoms include:

- Diarrhea, which may range from mild and watery to severe and bloody
- Stomach cramping, pain or tenderness
- Nausea and vomiting, in some people

CAUSES: ^[15]

Only a few strains of *E. coli* trigger diarrhea. The *E. coli* O157:H7 strain belongs to a group of *E. coli* that produces a powerful toxin that damages the lining of the small intestine. This can cause bloody diarrhea. You develop an *E. coli* infection when you ingest this strain of bacteria.

Unlike many other disease-causing bacteria, *E. coli* can cause an infection even if you ingest only small amounts. Because of this, you can be sickened by *E. coli* from eating a slightly undercooked hamburger or from swallowing a mouthful of contaminated pool water.

Potential sources of exposure include contaminated food or water and person-to-person contact.

Contaminated food ^[16-18]

The most common way to get an *E. coli* infection is by eating contaminated food, such as:

- **Ground beef.** When cattle are slaughtered and processed, *E. coli* bacteria in their intestines can get on the meat. Ground beef combines meat from many different animals, increasing the risk of contamination.
- **Unpasteurized milk.** *E. coli* bacteria on a cow's udder or on milking equipment can get into raw milk.
- **Fresh produce.** Runoff from cattle farms can contaminate fields where fresh produce is grown. Certain vegetables, such as spinach and lettuce, are particularly vulnerable to this type of contamination.

Contaminated water ^[19]

Human and animal stool may pollute ground and surface water, including streams, rivers, lakes and water used to irrigate crops. Although public water systems use chlorine, ultraviolet light or ozone to kill *E. coli*, some *E. coli* outbreaks have been linked to contaminated municipal water supplies.

Private water wells are a greater cause for concern because many don't have a way to disinfect water. Rural water supplies are the most likely to be contaminated. Some people also have been infected

with *E. coli* after swimming in pools or lakes contaminated with stool.

Personal contact ^[19]

E. coli bacteria can easily travel from person to person, especially when infected adults and children don't wash their hands properly. Family members of young children with *E. coli* infection are especially likely to get it themselves. Outbreaks have also occurred among children visiting petting zoos and in animal barns at county fairs.

E. coli can affect anyone who is exposed to the bacteria. But some people are more likely to develop problems than are others. Risk factors include:

- **Age.** Young children and older adults are at higher risk of experiencing illness caused by *E. coli* and more-serious complications from the infection.
- **Weakened immune systems.** People who have weakened immune systems — from AIDS or from drugs to treat cancer or prevent the rejection of organ transplants — are more likely to become ill from ingesting *E. coli*.
- **Eating certain types of food.** Riskier foods include undercooked hamburger; unpasteurized milk, apple juice or cider; and soft cheeses made from raw milk.
- **Time of year.** Though it's not clear why, the majority of *E. coli* infections in the U.S. occur from June through September. ^[20-22]
- **Decreased stomach acid levels.** Stomach acid offers some protection against *E. coli*. If you take medications to reduce stomach acid, such as esomeprazole (Nexium), pantoprazole (Protonix), lansoprazole (Prevacid) and omeprazole (Prilosec), you may increase your risk of an *E. coli* infection.

COMPLICATIONS ^[23]

Most healthy adults recover from *E. coli* illness within a week. Some people — particularly young children and older adults — may develop a life-threatening form of kidney failure called hemolytic uremic syndrome.

PREVENTION: ^[24]

No vaccine or medication can protect you from *E. coli*-based illness, though researchers are investigating potential vaccines. To reduce your chance of being exposed to *E. coli*, avoid swallowing water from lakes or pools, wash your hands often, avoid risky foods, and watch out for cross-contamination.

Risky foods

- **Cook hamburgers until they're 160 F (71 C).** Hamburgers should be well-done, with no

pink showing. But color isn't a good guide to know if the meat is done cooking. Meat — especially if grilled — can brown before it's completely cooked. Use a meat thermometer to ensure that meat is heated to at least 160 F (71 C) at its thickest point. [25-28]

- **Drink pasteurized milk, juice and cider.** Any boxed or bottled juice kept at room temperature is likely to be pasteurized, even if the label doesn't say so. Avoid any unpasteurized dairy products or juice.
- **Wash raw produce thoroughly.** Washing produce may not get rid of all *E. coli* — especially in leafy greens, which provide many places for the bacteria to attach themselves to. Careful rinsing can remove dirt and reduce the amount of bacteria that may be clinging to the produce.

Avoid cross-contamination

- **Wash utensils.** Use hot soapy water on knives, countertops and cutting boards before and after they come into contact with fresh produce or raw meat.
- **Keep raw foods separate.** This includes using separate cutting boards for raw meat and foods, such as vegetables and fruits. Never put cooked hamburgers on the same plate you used for raw patties. [29-30]
- **Wash your hands.** Wash your hands after preparing or eating food, using the bathroom, or changing diapers. Make sure that children also wash their hands before eating, after using the bathroom and after contact with animals.

MATERIAL AND METHODS:

Study design:

Study population: 62

Study period:

Study site:

Population and data collection

We performed a multicentre observational study with cases prospectively accumulated through the paediatric meningitis surveillance community **STUDY PERIOD**. This community blanketed records from 62 paediatric wards working with 2 microbiology departments. We used the seize-recapture method previously published in 2006, which estimated the completeness of the machine at 61% [132]. For this health facility-based active surveillance, 3 times a year, a medical investigator in every participating ward turned into contacted for information on new cases or to verify the shortage of such cases [133]. The records collection become authorised by way of the National Data Protection Commission. Data were prospectively amassed.

All neonates (<1 month of age) and infants (<one year of age) with a showed diagnosis of *E. Coli* meningitis were covered. The prognosis of meningitis was primarily based on as a minimum one of the following: fantastic CSF subculture, presence of superb soluble antigens in CSF, effective PCR consequences for CSF and/or fine blood culture related to pleocytosis (≥ 30 cells/ μ L) in CSF.

The following affected person characteristics have been accumulated: intercourse, gestational age at beginning (<32 weeks, very preterm; 32 to 36 weeks + 6 days, moderate to late preterm; ≥ 37 weeks, term), birth weight, postnatal age and weight at diagnosis and underlying conditions. Early-onset, late-onset and very late-onset diseases were defined as ≤ 6 , 7–89 and ≥ 90 days of age, respectively. The results of lumbar puncture (LP) were recorded (cell count, CSF glucose/blood glucose ratio and CSF protein value), along with microbiologic data (presence of K1 antigen, amoxicillin, cephalosporin's and nalidixic acid susceptibility of *E. Coli* strains). Concerning cephalosporin's treatment, we recorded the doses used, duration of treatment and delay between diagnosis and adjunct cephalosporin's therapy. Early treatment with cephalosporin's was defined as starting ≤ 2 days after LP and late treatment as cephalosporin's added > 2 days after LP. Cephalosporin's become the handiest fluoroquinolone provided [134].

Infants had been divided into two organizations with one group with use of cephalosporin's and other group not taking cephalosporin's. Patients with missing information for disorder severity at diagnosis, outcome or treatment were excluded from the analysis, as had been patients who did no longer acquire antimicrobial therapy with a 3GC and patients inflamed with *E. Coli* producing an extended-spectrum β -lactamase.

Variables collected are listed in Supplementary Table S1. There changed into no standardized definition for neurologic complications, which the clinician stuffed in a questionnaire in an open phase.

The number one final results was the percentage of brief-time period neurologic complications with versus without cephalosporin's. Short-time period neurologic headaches included seizures (considered as a complication through the clinician), strokes and thrombophlebitis, empyema, abscesses, intracranial high blood pressure or intraventricular bleeding or hydrocephalus and pachymeningitis or arachnoiditis.

Secondary outcomes have been mortality charge with and with out cephalosporin's; percentage of CSF sterilization failure with and with out cephalosporin's; and share of short-term neurologic headaches for patients with cephalosporin's remedy at some stage in the primary 2 days after LP (early

treatment institution) as opposed to without cephalosporin's.

Statistical evaluation

Categorical variables have been as compared by way of chi-square check or the Fisher actual test, and non-stop variables by means of the Student t check. To follow the reporting pointers on propensity rating (PS) evaluation^[135], for every outcome, we carried out exclusive methods to regulate for imbalance between the remedy groups. First, we presented results from a multivariate logistic regression, in which all variables which had been doubtlessly related to the outcome on univariate analysis ($p < 0.2$) were brought as covariates inside the model. Second, we finished a PS matched evaluation. Variables taken into consideration inside the univariate evaluation have been gestational age at birth, postnatal age at prognosis, beginning weight, weight at prognosis, sex, severity at analysis, CSF/blood glucose ratio <0.1 , CSF cell depend and CSF protein value. The PS approach attempts to stability treated and nontreated agencies in order to lessen confounding through indication in observational designs, thereby developing a quasirandomized test^[136].

Covariates that could be associated with final results or allocation to cephalosporin's treatment institution (clinically applicable or chosen through univariable evaluation) were used to generate the PS: gestational age at birth, postnatal age at diagnosis, beginning weight, weight at analysis, sex, seizures before remedy, coma, mechanical ventilation, shock, CSF/blood glucose ratio <0.1 , CSF cellular remember and CSF protein cost.

Patients receiving 3GC monotherapy had been then matched to the ones receiving mixture therapy with a 3GC and cephalosporin's via their PS through the use of 1:1 nearest-neighbor matching without alternative, with a minimum caliper of 0.25. Multivariate regression analysis became computed with uncooked statistics and no imputation; certainly, due to the fact a bias with a couple of imputation is possible, we chose to carry out multivariate analysis on subjects without lacking statistics as a way to examine the outcomes of both analysis. In order to restriction the variety of topics excluded from the regression analysis and to keep away from lowering the have a look at's power, we created a 'missing cost' class for variables with a big quantity of lacking statistics^[137-139].

Statistical evaluation became performed with the aid of Stata thirteen (StataCorp, College Station, TX, USA) and R 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-task.Org/>). Two-sided $p < 0.05$ turned into considered statistically sizable.

RESULTS AND DISCUSSION:

Characteristics of study population

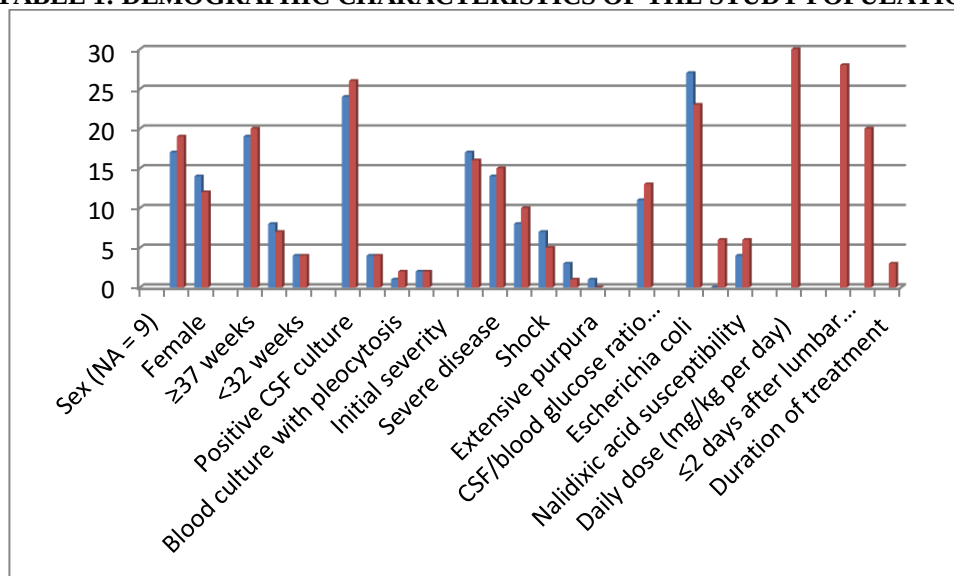
Between Study period, a total of 98 paediatric meningitis cases were reported. In this of children, 62 (63.2%) of 98 had a diagnosis of *E. coli* meningitis and they were further calssified as cephalosporin users and non cephalosporin user, i.e 31 in each group 62 (99%) of 62 were <12 months of age.

TABLE 1: DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

Demographic characteristics	No ciprofloxacin (n = 31)	Ciprofloxacin (n = 31)
Weight at diagnosis (kg) (NA = 99)	3.4 $\pm$ 0.66	3.43 $\pm$ 0.86
Sex (NA = 9)		
Male	17(54)	19 (60.4)
Female	14 (46)	12 (39.6)
Gestational age (NA = 12)		
≥ 37 weeks	19 (62.2)	20(63.9)
32–36 + 6 weeks	8 (25)	7 (23)
<32 weeks	4 (12.8)	4 (13.1)
Diagnosis (NA = 0)		
Positive CSF culture	24(79.5)	26 (83.6)
Positive soluble antigen	4 (12.4)	4 (12.9)
Blood culture with pleocytosis	1 (3.5)	2(5)
Positive CSF PCR results	2 (4.6)	2 (2.5)
Initial severity		

Nonsevere disease	17(56)	16 (51.7)
Severe disease	14 (44)	15(48.3)
Assisted ventilation	8 (27.1)	10 (31.3)
Shock	7 (22.3)	5 (17.4)
Seizures before treatment	3 (8.4)	1 (10.4)
Extensive purpura	1 (1.2)	0 (0)
Lumbar puncture results		
CSF white blood count	1689 (3–52000)	223600 (0–250000)
CSF protein level (g/L)	1.98 (0–17.4)	2.36 (0.44–20.5)
CSF/blood glucose ratio <0.1/total	11 (35.4)	13 (43.5)
Microbiologic data		
<i>Escherichia coli</i>	27 (85.8)	23 (82.2)
Ciprofloxacin susceptibility:	0 (0)	6(5.3)
Nalidixic acid susceptibility	4 (3.9)	6 (18.7)
Ciprofloxacin treatment		
Daily dose (mg/kg per day)		30 (10–60)
Delay of adjunct therapy		
≤2 days after lumbar puncture		28 (88.8)
>2 days after lumbar puncture		20/178 (11.2)
Duration of treatment		3 (2–95)

TABLE 1: DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION



Among the 31 infants analysed, 17 (54.8%) received cotreatment with cephalosporin's. For 158, cephalosporin's was added less than 2 days after LP, whereas for 20 cephalosporin's was added later (Table 1). The median dose was 30 mg/kg per day (range, 10–60 mg/kg per day) by intravenous route in two or three divided doses. The median duration of cephalosporin's treatment was 6 days (range, 2–95 days). All infants received antimicrobial therapy with the 3GC: cefotaxime in 21 (68.4%), ceftriaxone in 3 (10.4%), cefotaxime switched to ceftriaxone in 6

(20.7%) and ceftazidime in 1 (0.5%). An aminoglycoside was prescribed for 29 (89.7%) infants, including 27 (88%) of in the cephalosporin's group versus 38 (91.6%) in the noncephalosporin's group (p 0.4). In the cephalosporin's group, 15 (48.3%) infants presented a sign of initial disease severity versus 14 (44%) in the noncephalosporin's group (p 0.4).

Cephalosporin's and neurologic complications

In our study, 7 (23.4%) infants had at least one short-term neurologic complication. The most

frequent complications were empyema or pericerebral collection (3, 9.3%), hydrocephalus, intraventricular haemorrhage or intracranial hypertension (2/367, 7.4%), and seizures (2/367, 6%), followed by stroke or thrombophlebitis (1/367, 3%), cerebral

abscess (1/367, 1.4%) and pachymeningitis or arachnoiditis (1/367, 1.1%). Overall, 9 (28.4%) of 31 infants in the cephalosporin's group had complications versus 5 (17.5%) of 31 without cephalosporin's.

Table 2: ASSOCIATION BETWEEN CEPHALOSPORIN TREATMENT AND ITS OUTCOME

Outcome	No ciprofloxacin (n = 31), n (%)	Ciprofloxacin (n = 31), n (%)	P value
Neurologic complications	5 (17.5)	10 (28.4)	0.02
Death	3 (9.6)	1(0.9)	0.4
CSF sterilization failure	4 (14.3)	4(11.3)	0.2
Outcome	No ciprofloxacin (n = 31)	Early ciprofloxacin (n = 31)	
Reduced Neurologic complications	5 (17.5)	9(27.8)	0.02

This association remained significant when considering the impact of the delay of adjunct cephalosporin's therapy on short-term neurologic outcome. Indeed, 5 (17.5%) of 31 infants without cephalosporin's treatment presented complications versus 9 (27.8%) of 31 with cephalosporin's treatment ≤ 2 days after LP (OR = 2.0; 95% CI, 1.1–3.7 with PS analysis) and versus 8 (26.8%) with cephalosporin's treatment ≤ 1 day after LP (OR = 3.1; 95% CI, 1.4–6.9). The association was not significant when considering infants with cephalosporin's treatment added at day 0 versus infants without cephalosporin's treatment (OR = 1.9; 95% CI, 0.7–5.0; p 0.17 with PS analysis).

Cephalosporins and mortality

We recorded 4 (10.5%) deaths in our cohort, 1 (0.9%) with cephalosporin's cotreatment and 3 (9.6%) of 31 without. According to classic multivariable logistic regression, only initial severity was significantly associated with death (OR = 42.5; 95% CI, 5.7–318.4; p < 0.001), along with gestational age at birth <32 weeks (OR = 2.6; 95% CI, 1.0–6.6; p 0.05). The results of PS matching analysis for mortality were consistent with the classic analysis, showing no significant association between cephalosporin's and mortality (OR = 0.7; 95% CI, 0.3–1.6).

Discussion:

This study represents a large cohort of infants with *E. coli* meningitis and assesses the effect of cotreatment with cephalosporin's on neurologic outcome. Our results suggest that adjunct cephalosporin's therapy at least does not prevent short-term neurologic complications. Indeed, we found a significant increase in neurologic complications in the cephalosporin's group

(28.4%) versus the noncephalosporin's group (17.5%).

Contrary to our results, a previous prospective study including 36 neonates reported better results when cephalosporin's was added to a 3GC for *E. coli* meningitis. Indeed, 93% of the 15 infants cotreated with cephalosporin's did not present any short-term complications compared to 43% of the 21 patients without adjunct cephalosporin's therapy [140]. This study was not randomized and did not adjust results for gestational age at birth or microbiologic data. Other studies reported on the efficacy of cephalosporin's for treating meningitis, abscesses and ventriculitis due to Enterobacteriaceae in infants and neonates [141] but these studies are case reports or case series.

Despite the theoretical advantages of cephalosporin's, it did not reduce neurologic complications in our cohort. One explanation might be that neurologic complications occur during the initial invasion phase of the disease, with cell and tissue lesions showing at the very beginning of the disease [142]. In a cohort of adults with suspected meningitis, 24% already had abnormal head computed tomographic scan results before LP, and thus before antimicrobial therapy [143]. Even with early treatment, neurologic complications such as abscesses, empyema or vascular complications might occur in the early hours of the disease. There is no clear explanation for how cephalosporin's could lead to more neurologic complications. Indeed, a risk of neurotoxicity has been reported with cephalosporin's but leading to seizures or behavioural disorders, which does not explain the higher number of cases of empyema or hydrocephaly [144]. Our study suggests a

clear absence of superiority of a combination therapy with cephalosporin's, but the apparent higher risk might come from residual confounding by indication.

Combination therapies are currently questioned in the literature; in particular aminoglycosides are increasingly being discouraged to treat Gram-negative bacteraemia and sepsis because of the lack of benefit on morbidity and mortality as well as increased rates of nephrotoxicity. Recent studies suggest the lack of superiority of combination therapies for Gram-negative bacteraemia in children. Retrospective studies concluded an absence of advantage of empirical and definitive therapy with β -lactam and aminoglycoside therapy versus β -lactam monotherapy (except to treat multidrug-resistant organisms); they even suggested a decrease in nephrotoxicity with monotherapy ^[145]. These results match those of a meta-analysis of adult patients that discouraged combination therapies (mostly with aminoglycosides) to treat bacteraemia and sepsis ^[146-48].

The strengths of this study are a large multicentre cohort with population-based data and consistent results from two different methods of analysis (multivariable logistic regression and PS). The findings were consistent for each outcome: short-term neurologic complications, mortality, short-term complications for infants with early cephalosporin's treatment and rate of CSF sterilization failure, which highlights the lack of benefit of cephalosporin's for *E. coli* meningitis.

This study has several limitations. First, given the observational design of our study, we cannot prove a causal relation. However, the use of PS analysis, specifically developed to reduce indication bias in therapeutic studies without randomization, mimics randomized studies by matching patients by baseline characteristics ^[149]. Thus, this statistical method strongly limited the risk of confounding by indication for observational designs. However, despite the large number of cofactors included in the PS analysis, we cannot completely exclude the existence of other hidden factors that could play a role in the confusion. An indication bias cannot be excluded for several reasons. Firstly, data on clinical features of patients such as shock were reported according to clinicians' expertise and not standardized on biomarkers such as blood lactate, leading to subjectivity in the reported data. Secondly, concerning cephalosporin's susceptibility, probably partly because of the long duration of the study (16 years), we only have data for a third of the cohort, and only four (3%) of 135 of *E. coli* strains were resistant to cephalosporin's. However, because quinolones are rarely prescribed for paediatric patients, the rate of *E. coli* resistant to

cephalosporin's is generally low. In 2016, according to the European Antimicrobial Resistance Surveillance Network, in the age group of 0 to 4 years, the proportion is 6.5% ^[150]. The third limitation is the missing data on the timeline between adjunct cephalosporin's therapy and the appearance of neurologic complications, which can bring confusion to the results (there were more infants with complications in the cephalosporin's group). Among the infants receiving cephalosporin's, 88.8% received treatment initially and 11.2% secondarily, possibly after the complications had occurred, which increases the number of infants with complications in the cephalosporin's group. However, when looking at early-treated versus nontreated infants, the association between cephalosporin's and complications remains. Another limitation is the absence of standardization of neurologic complications' assessment and the absence of data on the timing of onset of complications. Because of the absence of guidelines on this aspect of follow-up, type (head ultrasound, head computed tomography or magnetic resonance imaging) and timing of neuroimaging were performed according to the clinician's decision and to the protocol used at each hospital. We did not have data either on the number of patients who underwent brain imaging or on the type of imaging conducted. Finally, results were not adjusted by centre, which can be a possible confounding factor. However, patients from the same centre did not necessarily receive the same treatment, with a median proportion of cephalosporin's use per centre of 50% (interquartile range, 33–83%) arguing against a centre effect.

For all these reasons, and because cephalosporin's treatment was initiated by clinician decision and not by following specific guidelines, we cannot exclude the notion that patients treated with additional cephalosporin's had more severe features, thus explaining the worse outcome in those patients and explaining why our study did not capture these differences. Nevertheless, these limitations would probably not change the conclusion that adjunctive cephalosporin's treatment does not appear to be beneficial. Data on long-term outcome and on cephalosporin's treatment tolerance were not available for our cohort.

CONCLUSION:

This study of a large cohort of infants with *E. coli* meningitis suggests that ciprofloxacin added to a 3GC at least offers no advantage in terms of improving short-term neurologic outcomes and mortality. However, when looking at early-treated versus nontreated infants, the association between cephalosporins and complications remains. The limitation is the absence of standardization of

neurologic complications' assessment and the absence of data on the timing of onset of complications. Because of the absence of guidelines on this aspect of follow-up, type (head ultrasound, head computed tomography or magnetic resonance imaging) and timing of neuroimaging were performed according to the clinician's decision and to the protocol used at each hospital. We did not have data either on the number of patients who underwent brain imaging or on the type of imaging conducted.

REFERENCES:

1. "coli". Oxford English Dictionary (Online ed.). Oxford University Press. (Subscription or participating institution membership required.)
2. Wells, J. C. (2000) Longman Pronunciation Dictionary. Harlow [England], Pearson Education Ltd.
3. Tenaillon O, Skurnik D, Picard B, Denamur E (March 2010). "The population genetics of commensal *Escherichia coli*". *Nature Reviews. Microbiology*. **8** (3): 207–17.
4. Singleton P (1999). *Bacteria in Biology, Biotechnology and Medicine* (5th ed.). Wiley. pp. 444–54.
5. "Escherichia coli". CDC National Center for Emerging and Zoonotic Infectious Diseases. Retrieved 2 October 2012.
6. Vogt RL, Dippold L (2005). "Escherichia coli O157:H7 outbreak associated with consumption of ground beef, June–July 2002". *Public Health Reports*. **120** (2): 174–78.
7. Martinson JNV, Walk ST (2020). "Escherichia coli residency in the gut of healthy human adults". *EcoSal Plus*. **9** (1).
8. Bentley R, Meganathan R (September 1982). "Biosynthesis of vitamin K (menaquinone) in bacteria". *Microbiological Reviews*. **46** (3): 241–80.
9. Hudault S, Guignot J, Servin AL (July 2001). "Escherichia coli strains colonising the gastrointestinal tract protect germfree mice against *Salmonella typhimurium* infection". *Gut*. **49** (1): 47–55.
10. Reid G, Howard J, Gan BS (September 2001). "Can bacterial interference prevent infection?". *Trends in Microbiology*. **9** (9): 424–28.